**REMARKS**

The Office Action of September 16, 2009 constitutes a non-final rejection of the claims. The Office Action and the references relied upon therein have been carefully reviewed. Reconsideration and allowance of the claims are requested in view of the foregoing amendments and the following remarks.

## I. Claim Status and Amendments

Claims 1, 3, 5, 7, 8, and 54-57 were pending in this application when last examined and stand rejected. No claims have been allowed.

By way of the amendment, new dependent claims 58-60 have been added. Support can be found throughout the disclosure in general. See, for instance, the disclosure at page 11, lines 1-12, page 13, lines 18-19, page 14, line 18 and lines 26-32, and also Example 5 on pages 34-35, for the amendment to claim 54 and new claim 58. See also Example 6 on pages 36-37 for new claim 59. See also the disclosure in in the last paragraph on page 14, for new claim 60. It is believed that the specification provides explicit and/or implicit support for the amended claim language.

Claims 1, 3, 5, 7, 8, and 54-60 are pending upon entry of this amendment, and these claims define patentable

subject matter warranting their allowance for the reasons discussed herein.

## II. Prior Art Rejections

Carpenter as evidenced by Baumann et al.

Claims 1, 3, 5, 7, 8, and 54-57 have been rejected under 35 U.S.C. 102(b) as being anticipated by Carpenter (WO01/88104) as evidenced by Baumann et al. (Physol. Rev. 2001, 81:871-927) for the reasons set forth in item 5 on pages 3-8 of the Office Action. This rejection is respectfully traversed. The arguments set forth in the response filed July 2, 2009 are reiterated herein by reference.

As best as can be understood by Applicants, the Examiner has maintained the rejection on the basis that as long as the prior art culture medium includes a gp130 activator and as long as $O1^+$ and/or $O4^+$ oligodendrocytes are produced, starting with cells that are derived from ES cells, the claims are inherently anticipated. The Examiner states that the method in the prior art references "uses the same claimed materials, the same active agents and the same active steps as in the claimed method of the instant claims" and that the "instant claims do not encompass or claim different active materials and steps from those taught in the prior art." The Examiner argues that the Applicants have not provided any

evidence to show any differences between the ingredients and methods used and the results obtained. In this regard, the Examiner contends that Applicants have not provided any evidence showing that the embryoid bodies of Carpenter are different from the neurospheres of the claims. In fact, on page 7, the Examiner states that "the embryoid bodies are neurospheres." In making these arguments, it is clear that the Examiner relies heavily on a theory of inherency in making and maintaining the rejection.

Applicants respectfully disagree and submit that Carpenter fails to expressly or inherently disclose each and every element of the claims. In this regard, the MPEP at §2112 explains the requirements of a rejection based on inherency. The MPEP at §2112 IV states:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is **necessarily present in the thing described in the reference**, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain

> thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). [Emphasis added.]

The MPEP at §2112 IV further states:

> "In relying upon the theory of inherency, **the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art**." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). [Emphasis added.]

Applicants respectfully submit that the allegedly inherent features are **not necessarily present** in the prior art teachings of Carpenter (as evidenced by Baumann et al.), or even in Gearhart et al. for that matter, for at least the following reasons.

First, a significant difference between the claimed process and that of Carpenter (and also Gearhart) is the starting material. The instant claims require that the starting material is neurospheres. But Carpenter does not start with neurospheres. Instead, the starting material in Carpenter (page 19, as referred to by the Examiner) is embryoid bodies (hereinafter "EBs"). Nonetheless, the Examiner argues that Applicant fails to provide evidence to show that the NS cells or cells derived from EBs of Carpenter

are different from the claimed NS cells. On page 7 of the Office Action, the Examiner even states that "the embryoid bodies are neurospheres." Applicants disagree.

Based on a review of the specification and the scientific literature as discussed herein, it is clear that the EBs of Carpenter are not the same as neurospheres. EBs are aggregates of cells derived from embryonic stem cells. EBs comprise a large variety of differentiated cell types; they first form a ball of cell and then take on a more complex appearance with different layers of structure containing different cells. This is supported by the disclosure of the instant application. See for instance, the bottom page 11, wherein it is disclosed that EBs include primitive endoderm and ectoderm layers. See also the discussion in Carpenter at page 11 lines 31-32, which describes the EBs as a heterogeneous cell population. By contrast, neurospheres are a free floating structures generated by neural stem cells. They do not include the primitive endoderm and ectoderm layers of EBs. Neurospheres are more homogenous in structure and cell type. Also, in Carpenter, the EBs are allowed to differentiate into neural precursors with various differentiation factors (see page 19, lines 30-31 of Carpenter). The neurospheres and the method of the present claims are different.

It should be noted that Carpenter knows what a neurosphere is. Carpenter mentions them on page 16, line 20, in discussing the type of gene expression analyses that can be done using the invention in Carpenter. However, if Carpenter were using his differentiation factors to further differentiate neurospheres, Carpenter would have said so. Indeed, Carpenter did not do so.

Further, as disclosed in the specification neurospheres can be obtained from EBs. The specification discloses that human embryonic stem cell lines derived EBs can form neural tube like rosettes expandable as floating neurospheres. The specification discloses methods for obtaining the neurospheres from EBs. For instance, the present application at page 13 explains how to isolate floating spheres in defined medium and then expand them as neurospheres. See also the references cited a page 13, lines 18-19 of the specification, and in particular Zhang et al. (2001) (a copy of which was previously submitted). See also the disclosure at page 14, lines 10-22, which describes isolating neurospheres from EBs. Based on this disclosure, it should be clear that EBs are not neurospheres, as the neurospheres must be expanded from floating spheres that were picked from the EBs (page 14, line 18).

Thus, contrary to the Examiner's position, neurospheres are not the same as EBs, even though they can be obtained from EBs. Again, neurospheres are more homogenous in structure and cell type, since they comprise neural stem cells, as opposed to EBs that contain numerous cell types. There is also no disclosure that the neural precursor cells of Carpenter are the neurospheres discussed in the present specification and described as "neurotube-like rosettes" in the Zhang et al. (2001) publication discussed in the specification (again a copy of which was previously submitted). See reference thereto in the present specification, for example, at page 10, lines 9-10, at page 13, lines 18-19, and at page 30, line 10. Thus, in view of the above, it should be clear that **EBS are not neurospheres** and *vice versa*.

Further, given that Carpenter does not disclose or suggest selecting neurospheres from the large variety of cell types present in EBs, it follows then that neurospheres are **not necessarily present** in the cells disclosed and used in the methodology of Carpenter. For these reasons, the Examiner's inherency argument fails, because the allegedly inherent feature (i.e., neurospheres) are **not necessarily present** in Carpenter. Consequently, Carpenter cannot be said to disclose, either expressly or inherently, each and every

element of claim 1. Therefore, Carpenter cannot anticipate claim 1.

To further emphasize this point and to expressly exclude other cell types, see new dependent claim 58, which specifies that "only NS cells are present in the growing in the culture medium step" of claim 1.

See also new claim 59, which calls for the use of dissociated NS cells in the growing in the culture medium step of claim 1 (support in Example 6 on pages 36-38). Certainly, if Carpenter fails to disclose the use of neurospheres, then Carpenter also fails to disclose the alternative embodiment in new claim 59. In this regard, nowhere does Carpenter disclose using neurospheres (claim 1), let alone cells isolated from neurospheres (new claim 59).

Second, as argued in the response filed July 2, 2009, main claim 1 specifies that the recited method specifically enhances differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. As such, the claimed method predominantly results in preferential differentiation into $O1^+$ and/or $O4^+$ oligodendrocytes. It does not result in production of the "mixture of cells" as disclosed in Carpenter and as acknowledged by the Examiner. See the Examples in the

disclosure, which show that the differentiation in accordance with the present invention is preferential toward oligodendrocytes, as opposed to the other lineages of neuronal progenitor cells. By contrast, Carpenter's method results in a heterogeneous mixture of cells. Yet, the Examiner was not persuaded by such arguments in the last response that Carpenter and Gearhart do not disclose specific differentiation into oligodendrocytes, because the methods in the prior art result in a mixture of cells. The Examiner contends that the specification fails to show that the claimed method only generates pure and homogenous O1+ and/or O4+ oligodendrocytes.

In reply, Applicants respectfully submit that the specification need not show the claimed method only generates pure and homogenous O1+ and/or O4+ oligodendrocytes, because it is believed that the method in Carpenter would not result in such oligodendrocytes, as claimed. In this regard, Applicants direct the Examiner's attention to Example 5 on pages 35-36 of the instant application. Example 5 investigates IL6RIL6 enhancement of oligodendrocyte lineage-specific gene expression. See specifically, page 35, line 31 to page 36, line 5. When EB cultures were treated with IL6RIL6, it resulted in little to no expression, as shown in Figure 2, lines 1-2. By contrast, when neurospheres were treated with IL6RIL6, it resulted in marked increase in expression. As

stated at page 36, lines 9-11, "[t]hese gene expression profiles support the conclusion that gp130 activator exerts enhancing effects on early phases of cell differentiation along the oligodendrocyte lineage (as denoted by Sox-10 and Olig-1 expression), as well as on them maturation toward myelinating MBP-expression oligodendrocytes."

It is respectfully submitted that this Example is clear evidence that the gp130 activator does not exert the same effect on EB cultures as it does on neurospheres. It follows then that the method in Carpenter, which utilizes EBs, would not produce the same result, as the claimed method, which utilizes neurospheres. This in turn is evidence that the method utilizing EB cultures of Carpenter does not result in enhancing differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes, because as shown in Example 5, EB cultures do not result in such preferential enhancement when treated with a gp130 activator. Also, the evidence in Example 5 further demonstrates that EBs are not neurospheres and *vice versa*.

For these reasons, it should be clear that the teaching in Carpenter does not anticipate the claims.

Furthermore, Applicants respectfully submit that the language in claim 1 requiring this preferential differentiation seemingly excludes the prior art teaching of Carpenter resulting in the mixture of cells.

In fact, it should be noted that nowhere does Carpenter disclose the use of a culture medium in a method to specifically enhance differentiation to cause the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. Instead, as argued in the last response, Carpenter relates to differentiation into a **mixture** of neuronal cells in general. Also, as noted in the last response, there is no example in Carpenter of specific differentiation into oligodendrocytes. In Example 3, a cocktail of differentiation factors was used to cause A2B5-positive cells to mature into neural cells that include oligodendrocytes, astrocytes and also a large proportion of neurons. Note that only about 13% of the mature cells were GalC positive, indicating that they may be oligodendrocytes. CNTF was only one of six factors that were used.

Accordingly, as Carpenter does not begin with neurospheres and the culture medium of Carpenter does not promote the preferential differentiation of NS cells into a oligodendrocyte lineage as recited in the claims, none of the present claims are anticipated by Carpenter.

Furthermore, claims 56 and 57 specify that "said culture medium promotes myelinating activity" and "said culture medium resulted in formation of large and highly branched $O1^+$ and/or $O4^+$ oligodendrocytes exhibiting large myelin membranes", respectively. Support can be found in the disclosure at page 36, lines 30-33 (Example 6) and at page 37, lines 29-32 (Example 7). Carpenter does not disclose these newly claimed features.

For these reasons, it is clear that Carpenter fails to disclose each and every element of the claims, as required for anticipation. Therefore, Carpenter cannot anticipate the claims.

Therefore, reconsideration and withdrawal of this rejection are respectfully urged.

Gearhart et al. as evidenced by Baumann et al.

Claims 1, 3, 5, 7, 8, and 54-57 have been rejected under 35 U.S.C. 102(b), as being anticipated Gearhart et al. (US 6,562,619), as evidenced by Baumann for the reasons set forth in item 6 on pages 8-9 of the Office Action. This rejection is respectfully traversed for the same reasons set forth above with respect to the arguments against Carpenter.

Similar to Carpenter, Gearhart fails to disclose the use of neurospheres. The word neurospheres nowhere appears in in the disclosure of Gearhart. For the reasons set forth

above and reiterated herein by reference, a neurosphere cell is distinctly different from an Eb, as is disclosed in Gearhart. In this regard, the instant application discloses that the NS cells are derived from embryoid bodies and the Zhang et al (2001) reference referred to in the specification specifically teaches how to obtain NS cells from embryoid bodies. The Examiner's reference to a discussion of embryoid bodies says nothing about differentiation of neurospheres as claimed.

For these reasons, Gearhart cannot be said to anticipate the claims.

Further, as discussed above, the present claims specify that they are specifically enhancing differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. Gearhart does not disclose this. Gearhart fails to disclose a culture medium that promotes the preferential differentiation into oligodendrocytes as claimed. Gearhart only teaches generalized differentiation and does not teach how to obtain preferential differentiation into oligodendrocytes.

For these reasons, Gearhart cannot anticipate the claims. Reconsideration and withdrawal of this rejection are also respectfully urged

**III. Indefiniteness Rejections**

Claims 54 and 55 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite, for the reasons in item 7 on pages 9-11 of the Office Action. This rejection is respectfully traversed.

As to the indefiniteness rejection of claim 54, the Examiner appears to be concerned about the fact that Applicants are trying to claim the gp130 activator as the sole growth agent while the claimed culture media must have other growth agents in them as well. However, the Examiner provides no basis to support this assertion.

Further, as discussed in the last response, the noted claim language clearly requires that the one or more gp130 activators is the only growth or differentiation agent present in the culture medium. In effect, this language clearly specifies that the culture medium does not have other growth factors in it. Applicants fail to see how this is indefinite or somehow inconsistent. Certainly, Applicants can use culture medium that contains only the one or more gp130 activators recited in the claims. This claim language is clearly defined in the specification, in the last paragraph on page 14, where it states that the gp130 activator is added to the NS cells to promote formation of oligodendrocyte progenitors "either alone or together with other growth or

differentiation agents such as retinoic acid, EGF, PDGF etc." (Emphasis added). Again, it is believed that this language is clear on its face. It is not ambiguous, nor is it indefinite.

To further emphasize this point, Applicants have added new claim 60 that "said one or more gp130 activators is the only growth or differentiation agent present in the culture medium to cause NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes." This amendment further excludes other growth agents with the required properties from the claims.

As to the indefiniteness rejection of claim 57, the Examiner contends that it is unclear what is meant by "large" and "highly branched" $O1^+$ and/or $O4^+$ oligodendrocytes exhibiting "large" myelin membranes. Applicants respectfully disagree and submit that the skilled artisan would understand the metes and bounds of the noted claim terms "large" and "highly branched" in the phrase "large and highly branched $O1^+$ and/or $O4^+$ oligodendrocytes exhibiting large myelin membranes" as compared to normal oligodendrocytes based on the teachings in the disclosure and the knowledge in the field.

In this regard, as set forth in MPEP § 2173.02, definiteness of claim language is analyzed, not in a vacuum, but in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted

by one possessing the ordinary level of skill in the pertinent art. Moreover, it is well established that not all relative claim terminology is indefinite. In a discussion about "Relative Terminology", MPEP § 2173.05(b) states as follows:

> The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.

Moreover, MPEP § 2173.05(b) further states:

> When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree. If it does not, a determination is made as to whether one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention. [Emphasis added.]

In the instant case, the specification (at for instance page 30, lines 23-32, and in Examples 6-7 on pages 36-38) discloses that the present invention, as claimed, results in oligodendrocytes with more aborization (i.e., highly branched) and they grew to a much larger size than in control samples (without treatment by gp130 activators). The level of skill in the art is extremely high and the skilled artisan would

know the size of normal oligodendrocytes based on the knowledge in the field and the guidance in the disclosure. Thus, it is believed that the skilled artisan would clearly understand the terms "large" and "highly branched" with respect to $O1^+$ and/or $O4^+$ oligodendrocytes as compared to oligodendrocytes of normal size.

The claims are thus clear, definite and have full antecedent basis. This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

## VI. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action. It is respectfully submitted that the claims are in condition for allowance and favorable action thereon is requested.

In the event that the Examiner disagrees and maintains one or more of the rejections, then kindly contact the undersigned attorney at the telephone number below to discuss comments or proposals for expediting prosecution.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Jay F. Williams
Registration No. 48,036

JFW:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
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